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"Investigation of laser damage on skin by 1540 nm Er -glass laser".

Final Report

Contract F61708-94-C-0008

by

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FOREWORD

The research program whose results are presented in this report was initiated by the Armstrong Laboratory of United States Air Force, Brooks Air Force Base, Texas and was supported by European Office of Aerospace Research and Development, under Contract F61708-94-C-0008.

The research reported covered a period from September 16, 1994 to September 15, 1995. The study was held in the General Physics Institute of Russian Academy of Sciences. Dr.Alexei Lukashev served as project leader. Medical supervision was conducted by Dr.Valery Solovyev, M.D., and Dr.Victor Engovatov, M.D., from Center of Biophysics Research of Russian Health Ministry.

ABSTRACT

"Investigation of laser damage on skin by 1540 nm Er -glass laser".

OBJECTIVE:

To define skin response to different radiant exposure of short(nanosecond) and long(millisecond) laser pulses and reaction to multipulse action using Er-glass laser radiation(1540 nm).

METHODS:

Lesion ranging from a mild erythema to tissue coagulation were produced on porcine skin (*in vivo*). Radiant exposure producing 50 percent probability(ED50) of a particular grade of lesion were established. A dependence of ED50 of minimum erythema versus number of pulses and beam cross section were studied.

RESULTS AND CONCLUSION

The dose-response relationship for producing different grades of burns were determined for energy densities of single laser pulse within the range 0.5-35 J/cm^2 and pulse duration 100 ns and 2.5 ms. The single pulse dose in a chain of repetitive pulses producing minimum erythema were determined for 2^n(n=1-6) pulses. The minimum reaction of skin on laser irradiance were studied for different beam diameter(2-10 mm). The reaction of skin is mostly considered as local super heating. The data obtained are adequate to update safety standards for cutaneous injury within these ranges of radiant exposure and beam spotsize .

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I. INTRODUCTION

Eye-safe laser systems based on Er glass lasers(λ=1540 nm) have various applications in training facilities of the Air Force. In the previous safety standard (ANSI Z136.1-1986), Table 7(Skin Exposure Limits) had an exception for 1540 nm radiation, permitting 1 J/cm^2 for microsecond to nanosecond pulses. This exception was made, in part, because of high damage threshold that was found by researchers studying ocular damage[1,2]. In the revised Standard (ANSI Z136.1-1993), Table 7 (on Skin) removed the exception for 1540 nm for skin exposure, making it 0.01 J/cm^2. It means that lasers that are eye-safe may now be skin-hazardous. This great change of the Standard was done without substantial experimental data on interaction of 1540 nm laser radiation with human skin.

The research reported was undertaken to receive experimental data on interaction of 1540 laser radiation of an Er glass laser with skin in the wide range of laser energy fluences, pulse durations, and number of repetitive exposures.

II. METHODS

2.1 Laser System

In order to solve the task of studying the influence of pulsed 1540 nm laser radiation on skin in a wide range of energy densities and pulse durations we had to construct an original laser system operating in both free-run and Q-switched regimes. The basic optical setup of the installation is presented in Fig.1a.

The active rods of the laser were made of Er-activated phosphate-based glass which was designed and produced in General Physics Institute[3]. In order to enhance its efficiency under flashlamp pump operation the glass was co-doped by chromium and ytterbium ions. The rods used in the laser system had diameter of 6-7 mm, length 85-90 mm and AR coatings of both ends. The single-lamp pump cavity had narrow (1-1.5 mm) channels for water cooling of Xe flashlamp and glass rod. Narrow channels are required to reduce pump radiation absorption by water in the spectral band of ytterbium absorption (0.85 - 1.05 micrometers). This peculiarity of laser cavity design has made it possible to avoid cooling of the laser head by deuterised water and thus to reduce the cost of the laser system.

In the free-run regime the laser head was supplied with a flat 65% reflectivity output mirror. The output energy reached 6-8 J in multimode and the plug efficiency - 1.5 - 2 %. The pulse duration was about 3 ms (Fig.2).

To obtain Q-switched regime the laser output mirror was substituted by a frustrated total internal reflection (FTIR) optical shutter in combination with two highly reflecting at 1.54 micrometers flat mirrors[4]. This kind of shutters has been chosen due to its high optical damage threshold, low insertion losses in combination with low (100 V) driving voltage and insensitivity to laser beam polarization state. Our shutter consisted of a pair of truncated fused silica pyramids having a rigid connection with each other. The gap of about 0.5 micrometer wide between the pyramids can be rapidly collapsed to zero with the help of two piezoelectric cells mounted on the truncated facets of each pyramid (Fig. 1b). The output energy of Q-switched laser reached 0.5 J in multimode beam and pulse duration was about 100 ns. The temporal shape is shown in Fig.3. In experiments laser output parameters was monitored by pyroelectric detector PED(pulse duration) and by power meter PM (output energy)(Fig.1).

A tilted lens L is used to compensate non-uniformity of the pump and thermo-induced lens and astigmatisms in the laser rod. The density of the laser radiation on the target can be varied with the help of either pump variations or neutral filters, and also by changing the size of illuminated spot by varying the optical power of the focusing lens. The aiming and focusing of the laser beam on the target was made with the help of a pilot He - Ne laser beam coaxial with the Er-glass one. The beam shape on the object plane was round with diameter 2-10 mm for free running and 2-4.5 mm for Q-switched modes. The corresponding maximum energy fluence was up to 35 J/cm^2 for free running and 20 J/cm^2 for Q-switch modes.

2.2 Animals

In experiments we used white domestic pigs(a breed 'Krupnaya belaya' -'Big white') free of visible pigmentation. Pigs were selected because of histological resemblance of their skin to that of man. The pigs were 1.2-2 months old and weighted 8-16 kg. Pigs were got from pedigree farm nearby Moscow, all animals were healthy and passed standard medical treatment(vaccination) for their age.

During every experimental set one animal was kept at the GPI for one week. At the GPI animals were held in a separate room in special wooden box with sawdust pad. They were fed 2 times a day (bran + milk powder soluted in warm water). Animal maintenance and usage in experiments were supervised and approved by representative of independent commission from Biological Department of Moscow University. After termination of the experimental set the animals were passed to a farmer.

One day before the experiment the bristle on the animal's back and sides was removed with hand clippers and then shaved. No visible skin reaction(reddening, cuts, etc.) was observed on the skin at the time of experiments because of hair removing. The depilated area was divided into a grid of squares about 15x15 mm in size. A side of the animal could have up to 90 cells. In the morning before experimental procedure the animals were not fed.

During experiments we did not used any anesthetic agents, since we assumed possible influence of anesthesia to the skin reaction. We held a pig by hands to make it unmovabale during exposures. The animal kept itself rather quiet. Sometimes pigs flinched immediately after exposure like a reaction on pin prick. We consider that it was frightened by the sound of capacitors discharge in power supply since there was no correlation between such a reaction and energy fluence of laser pulse.

2.3 Experimental procedure

This study had several tasks. It was determination of lesion threshold and supra threshold effects on animal skin made during single pulse exposures; determination of dependence of minimal lesion dose upon number of pulses in multipulse exposure. The third task was determination the dependence of minimal lesion dose upon laser beam cross section. All experimental tasks included both free running and Q-switched mode.

The experimental set was started up with preliminary estimation of the ranges and values of dose which produce visible lesions. We started with maximum energy fluence determined by laser output parameters and then decreased the dose by step of 0.5-1 J/cm^2 . Five cells on the animals were exposed by the pulses with the same dose.

The skin reaction data was obtained by visual examination the areas exposed at several minutes, one-hour and at 24 hours post exposure. In general, the one-

minute reaction at a given radiant exposure level served as a guide in determining whether increased radiant exposure levels should be given. In general, a very mild erythematous reaction at one-minutes will probably fade at one-hour. This level would represent the lowest level to be used. A definite well demarcated erythematous reaction on the skin at one-minutes will probably be present at one-hour examination.

At one-hour, each area exposed was again visually controlled and photographed. The number of "reactions" (this could be erythema, papules, blanching, etc.) were determined at each exposure level. The burns were categorized independently by two investigators. A similar examination and photographs were done at 24 hours post-exposure. Experimental data were processed by the probit method of Litchfield and Wilcoxon[5] in Rot modification. This data, expressed as a percentage of the reactions observed at each exposure level, was plotted on probability scale and the radiant exposure at the 50 percent probability level was taken as the ED50 level.

In the subsequent experimental sets probability of specific skin response(see 3.1) in the range of transient reaction was determined more accurately. To do this we exposed up to ten cells with the same fluence close to threshold range in order to have more accurate statistical data. To obtain truly data and estimate deviation of individual reaction we conducted experimental set on three animals and then the results were averaged.

III. RESULTS

3.1 Damage threshold and supra threshold effects on pig's skin for single laser pulse.

Since in the experiments we did not make histological investigation of the exposed parts of the skin, we conventionally classified observable skin reaction into following five types, assuming that at minimum persistent lesions(no.2,3) only superficial epithelium structures of skin are damaged in the most of the cases.

1. Diffusive, transient erythema that appeared within a minute post exposure and usually extended beyond the limits of exposed. Within several or dozen minutes(< 1 hour) the diffusive reddening decreased in size disappeared entirely. This was the functional reaction of blood vessels to laser action.
2. The persistent lesion(erythema) of round flat form(which does not come over the surface of the skin) and red color. Its size corresponded to the size of laser beam.
3. Erythema as described in the previous grade with infiltration(inflation). The nidus protruded over uninjured skin.
4. Coagulation of subepidermal layers of dermis. The round almost flat nidus of white color with the very thin red circle of inflammation.
5. Coagulation of deeper layers of dermis. The round nidus of white color with strong protruded inflammation.

An illustration of skin reaction are given on Fig.4,5.

FREE RUNNING(Long pulse)

In the first set of experiments(Free running, τ=2.5 ms, the spotsize diameter 5.5 mm) the radiant exposure ranged from 1.1 J/cm^2 to 23 J/cm^2.

The statistically processed data for minimal erythema at 1 hour post-exposure are plotted at the Fig 6. ED50 at 1 hour post exposure was found to be 5.7±1.2 J/cm^2. 282 burns were processed.

ED50 at 24 hour post exposure 6.5 J/cm^2.
The skin reaction No. 3(erythema with inflation) started at 8 J/cm^2.
The skin reaction No.4 (flat coagulation) - 13 J/cm^2.
Coagulation of dermis - 22 J/cm^2.

Q-SWITCHING(Short pulse)

In the second set of experiments(Q-switch, τ=100 ns, the spotsize diameter 2.5-3.5 mm) the radiant exposure ranged from 1.7 J/cm^2 to 16 J/cm^2. The statistically processed data for minimal erythema at 1 hour post-exposure are plotted at the Fig 6. ED50 at 1 hour post exposure for persistent erythema was found to be 3.0 ± 1.1 J/cm^2. 266 burns was processed.
ED50 at 24 hour post exposure 3.5 J/cm^2 .
We did not clearly distinguish burns described in the No.3 of skin reaction.
The flat coagulation was at 9 J/cm^2.

The deviation of individual sensitivity of animals and skin at different places (back, closer to belly) in the both sets was within 15 % of obtained data.

The slope on probability plot(Fig.6) (slope= ED84/ED50=ED50/ED16[6]) is 1.5 for free running and 1.3 for Q- switch. The relatively high value of the slopes are indicative of small increase in dose required for the response to vary from no observed effect to the high probability of observing a response. This may be considered as a reason for assuming threshold character of skin reaction to that laser wavelength.

3.2 Skin damage resulting from exposure to multiple pulses.

The task of this part of the study was to determine dependence of ED50 of minimal erythema upon number of repetitive pulses.

The starting radiant exposure for single pulse was ED60-80(Fig.6) then it was decreased by 0.5 J/cm^2 until ED5-10 exposures. For the series with doubled pulses we started with the fluences a little bit less(5-10%) than with single pulse and decreased fluence as described previously. For the following series we decreased initial radiant exposure and increased number of pulses. In the serie the energy fluence was decreased until lesion probability was 5-10% just after exposure.

The experiments were made with 1, 2, 4, 8, 16, 32, 64 repetitive laser shots to the same area at different radiant exposure of single pulse. The maximum number of 64 pulses at the same place was explained by low repetition rate of the laser(0.1 Hz), the time of this experiment took about 10 min. and the most difficult was to hold the animal unmovable by hands during exposures. In the cases of long overall exposures(16,32,64 pulses) we used cells on the back of the animal close to the spine. With this arrangements the pig could lay down still on the pad in its most natural position for longer time. Since for long multipulse exposure the single pulse energy fluence was well below ED50 there was no visible reaction of the animal to laser shots. Some times during 64 pulses experiments it got asleep.

The skin reaction data was obtained by examining the areas exposed at several minutes, one-hour and at 24 hours post exposure. 5-10 cells were exposed to every value of laser fluence.

In the experiments we observed the following types of skin reaction:

1. Immediately following the exposure, the skin at the exposed site developed a diffusive, transient erythema that usually extended beyond the limits of exposed area.(up to 1 cm in diameter, much bigger than we observed with single pulses).

Within several or dozen minutes(< 1 hour) the diffusive reddening decreased and in the case of milder reactions disappeared entirely. This was the functional response of blood vessels to laser action.

2. In the case of long exposures (more than 16 pulses) a white spot with diameter close to that of laser beam appeared in the center. This white spot could either disappear or transform to erythema after 1 hour.
3. The persistent erythema of round flat form and red color which appeared after one hour. Its size corresponded to the size of laser beam

The value of radiant dose of single pulse for ED50 for free running (τ=2.5 ms, the spot diameter D=6.5 mm) at 1 hour and 24 hour post-exposure are presented in Table 1.

Table 1.

Number of pulses, N	ED50 at 1h PE, J/cm^2	ED50 at 24h PE, J/cm^2
1	5.4	5.5
2	4.8	4.9
4	3.6	3.8
8	2.8	2.9
16	2.5	2.7
32	1.5	2.0
64	1.0	1.5

In the second set of experiments laser operated in Q-switch (τ=100 ns, D= 3.5 mm). The value of ED50 dose of single pulse at 1 hour and 24 hour post-exposure are presented in Table 2.

Table 2.

Number of pulses, N	ED50 at 1h PE, J/cm^2	ED50 at 24h PE, J/cm^2
1	3.2	3.1
2	2.8	2.9
4	2.4	2.5
8	2.0	2.2
16	1.8	2.0
32	1.7	1.8
64	1.6	1.6

In both cases the deviation of individual sensitivity of animals and skin at different places (back, closer to belly) was within 10-15 % of obtained data. The data are presented in the plots with linear and logarithmic scales(Fig.7). The dependence of overall exposure $E_l = E_{sp}N$ (E_{sp}-energy fluence of single pulse) upon number of pulses N are proportional to $N^{0.58}$ for free running and $N^{0.82}$ for Q-switching mode. In the Fig.8b approximation curves of experimental data are hyperbolas. Extrapolating them to the higher pulse number it is possible to assume that there is minimal exposure dose of single pulse which does not produce visible lesion even in any long series of pulses. It is 0.8 J/cm^2 for free running and 1.1 J/cm^2 for Q-switching.

3.3 Dependence of ED50 upon cross section of laser beam.

During experiment ED50 value of minimal lesion was measured at various laser spot sizes on the animal skin. The maximum spot size was determined by maximum laser energy and energy fluence producing persistent lesion with 60-70% probability. In the case of free running the maximum laser energy was 7J, energy fluence 8 J/cm^2, thus maximum cross section was 0.9 cm^2(d< 11 mm). In the case of Q-switch E_{max} = 0.6 J, energy fluence 5 J/cm^2, S_{max} = 0.12 cm^2(d< 4 mm). The minimum spotsize was about 2 mm, because at spot diameter less than 2.5 mm we found it difficult to distinguish laser lesion due to inhomogenity of porcine skin. For the Q-switch mode we had rather small range of varying laser spotsize.

Determination of ED50 was conducted by the method described in 2.3. The results are presented in the Table 3.

	spot diameter d, mm	cross section S, cm^2	ED50 24h PE, J/cm^2
1.Free running			
	10	0.79	6.0
	5.6	0.25	7.0
	2.7	0.057	6.5
	2.0	0.028	6.8
2. Q-switch			
	4.2	0.14	4
	2.6	0.056	3.5

The deviation of individual sensitivity of animals and skin at different places (back, closer to belly) was 15 % in both cases. We considered that deviation of the obtained data are within the interval of individual and local sensitivity of the animal skin and there was no visual dependence of ED50 upon laser spotsize. The constant value of the ED50 in this experiment is explained by the geometry of the experiment and described in the next section.

IV. DISCUSSION

The skin response resulting from exposure at 1540 nm is considered to be a result of temperature elevation of the tissue. The clinical description of skin burns at 1540 nm is fairly coincides with that of at 10.6 μm of CO_2 laser[7,8]. The geometry of the experiment and estimation of the cooling of the exposed volume suggests weak influence of heat dissipation in our experiments, especially for short pulses (< 1 μs) (Fig. 8). The penetration depth h of laser light at 1540 nm to water is about 1 mm(the absorption coefficient $\alpha \approx 10$ cm^{-1} [6,11]), in the first approximation we consider that true for the skin too. The smallest laser beam diameter on skin was 2 mm and the largest 10 mm (long pulses: free running). Characteristic cooling time t_c of the layer thickness h could be estimated from formula $h \approx (\chi\ t_c)^{1/2}$, where χ- thermal diffusivity of water (χ = 1.4 10^{-3} cm^2/c). For water layer 1 mm thick which is equal to penetration of laser light into water t_c is equal 10 sec . The cooling time is much longer than pulse duration for both laser pulses(100 ns and 2 ms), only in the latter case some weak heat dissipation could be considered. If again to use water substance as a model for our experiment, the equivalent temperature rise $\Delta T = E_l/(Shc_p)$ is 8^0 C for short pulses and 15^0 C for long at ED50 dose; 20^0C and 34^0C respectively for coagulation. (E_l - laser energy, S - laser beam cross section, c_p - specific heat, c_p = 4.2 $J/(Kcm^3)$). Thus, the absolute temperature of the animal

skin is higher than 42-43^0 C which is close to the temperature of protein denaturation. The greater value of ED50 for longer pulses we explained by the influence of heat dissipation during the laser pulse.

The data obtained in our experiments for the skin are in a good agreement with data obtained earlier [1,2,6] for the cornea. In the case of cornea the steepness of lesion probability curve is higher and the ED50 for both short and long pulses are about 10-40% higher. This difference could be because that cornea has higher water content and the structure of corneal and skin melanin as well as their thermo-physical properties are different[10,12].

Dependence of ED50 on number of pulses is difficult to explain without good model, however we would like to make some comments. According to estimation made in the previous paragraph the cooling time of the exposed volume is about 10 sec. In the case when repetition rate of the laser is higher than 0.1 Hz the influence of addition of exposure dose of single pulses becomes more pronounced. In our experiments repetition rate was 0.1 Hz and the effect of addition of expose dose should not be so striking. Thus, obtained dependence of integral dose E_I ($E_I = E_{sp}N$) vs. number of pulses is valid only for repetition rate about 0.1 Hz. This dependence should be closer to N^1 (linear addition of radiant exposure of single pulses of the same fluence) for slower repetition rate or faster cooling of the exposed site and maybe decreasing(up to N^0 - constant integral dose equal to the value ED50 of single pulse) for high repetition rate and slow cooling.

The analysis of the data obtained in the experiment revealed that there was no dependence of ED50 parameter upon laser spot cross section within the range of available radiant exposure. This fact could be predicted from the consideration proposed above. Since we consider skin damage to be thermal, the local temperature could be a measure of the damage. Local temperature rise is determined by:

$$\Delta T = E_l / (Shc_p),$$

The rate of cooling is determined by $l_t = (\chi \ \tau_l)^{1/2}$ and dimensions of the experiment. In the framework of our consideration we can assume an increase of heated up volume due to thermal conductivity and thus decrease of local temperature as the first order approximation.

$$\Delta T' = E_l / (c_p(V + dV)) = E_l / (Shc_p)(1 - dV/V),$$

$$dV = d(Sh) = Sdh + hdS = Shdh/h + 2Shdr/r = V(l_t/h + 2l_t/r)$$

$$\Delta T' = E_l / (Shc_p)(1 - (l_t/h + 2l_t/r)),$$

This formula may determine the first order approximation of the dependence of ED50 on beam parameters. To have the same skin response on laser radiation $d(\Delta T')=0$, i.e. the same local temperature rise. Then the dependence of radiant exposure $\mathcal{E} = E_l/S$ upon laser beam parameters looks:

$$\mathcal{E} = const/(1 - (l_t/h + 2l_t/r)),$$

when $l_t << h,r$

$$\mathcal{E} = const(1 + (l_t/h + 2l_t/r))$$

The bigger r the closer we are to 1-D case with no dependence of ED50 upon laser beam parameters. In our set up the value of $l_t << h,r$, thus the absence of dependence of ED50 upon cross section seems rather reasonable. According this estimations one can clearly observe this dependence when r < 0.2 mm.

V. CONCLUSIONS

In this study we experimentally determined reaction of porcine skin(*in vivo*) to exposure by 1540 nm radiation of Er-glass laser. The persistent lesion of the skin in the range up to 35 J/cm^2 was classified. The ED50 value for minimal lesion was found to be 5.7 J/cm^2 for millisecond and 3.0 J/cm^2 for nanosecond laser pulses. The skin coagulation starts at 13 J/cm^2 for millisecond and 9 J/cm^2 for nanosecond pulses.

For multipulse action dependence of ED50 of minimal lesion vs. number of pulses was determined for repetition rate of the laser pulses 0.1 Hz. The dependence of overall dose is proportional to $N^{0.58}$ for free running and $N^{0.82}$ for Q-switch. It was found that there was minimal exposure dose of single pulse which does not produce lesion in multipulse action. It was 0.8 J/cm^2 for free running and 1.1 J/cm^2 for Q-switching. No dependence of ED50 vs. laser beam spotsize was found for beam diameter 2-10 mm.

The results obtained in this study are explained by simple consideration of light absorption at the surface of skin without substantial thermal dissipation.

We believe that data obtained in this work are adequate to update safety standards for cutaneous injury by 1540 nm laser radiation. Additional research of histology of the persistent lesions would be very helpful for more accurate classification of burns and could be used for possible applications of 1540 nm radiation for surface skin operations(cosmetic surgery).

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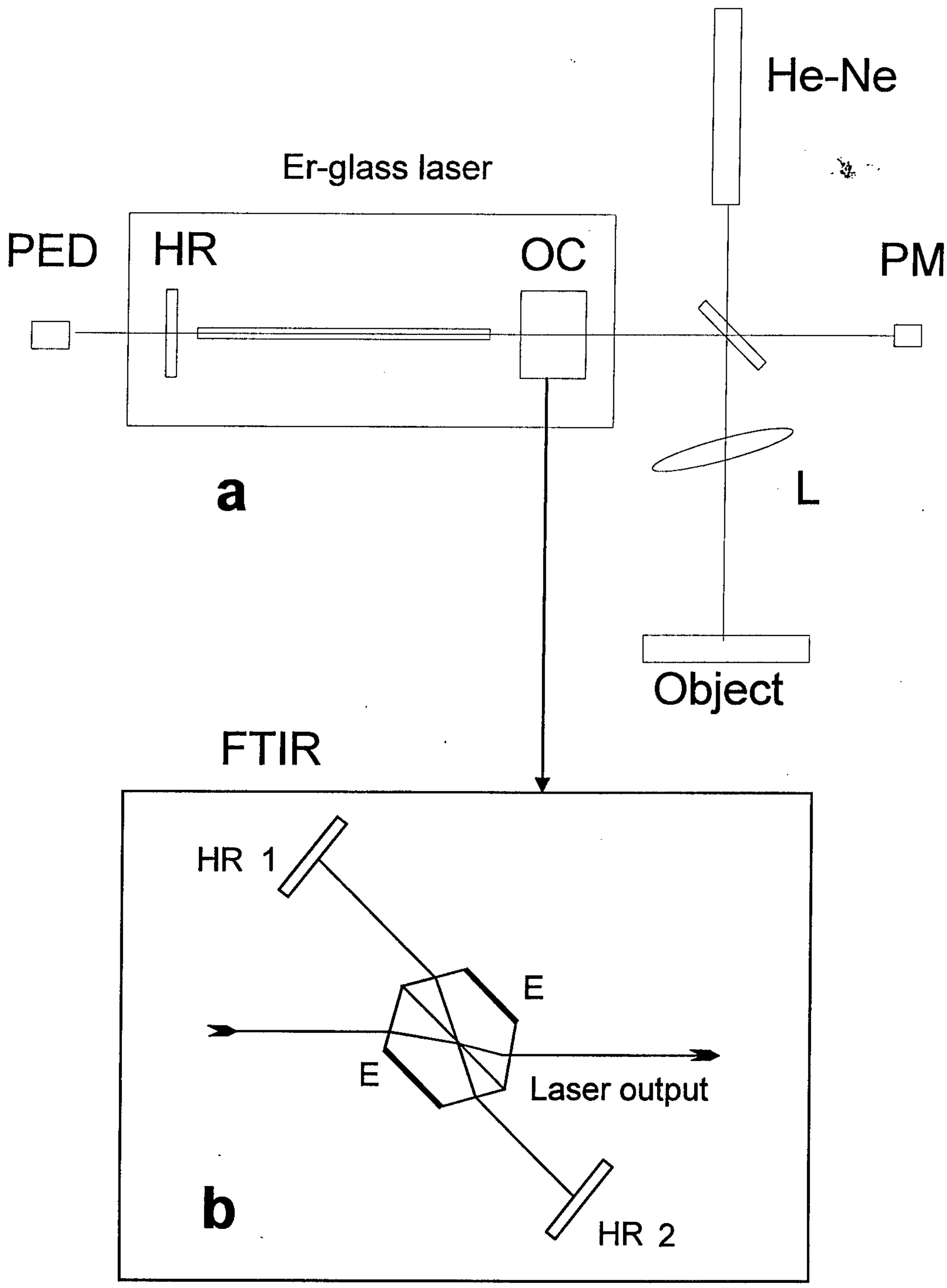


Fig.1. Experimental optical setup. HR-high reflecting mirror, OC-output coupler (a mirror for free running and FTIR modulator for Q-switching), PED- pyroelectric detector, PM-power meter, E-electrodes.

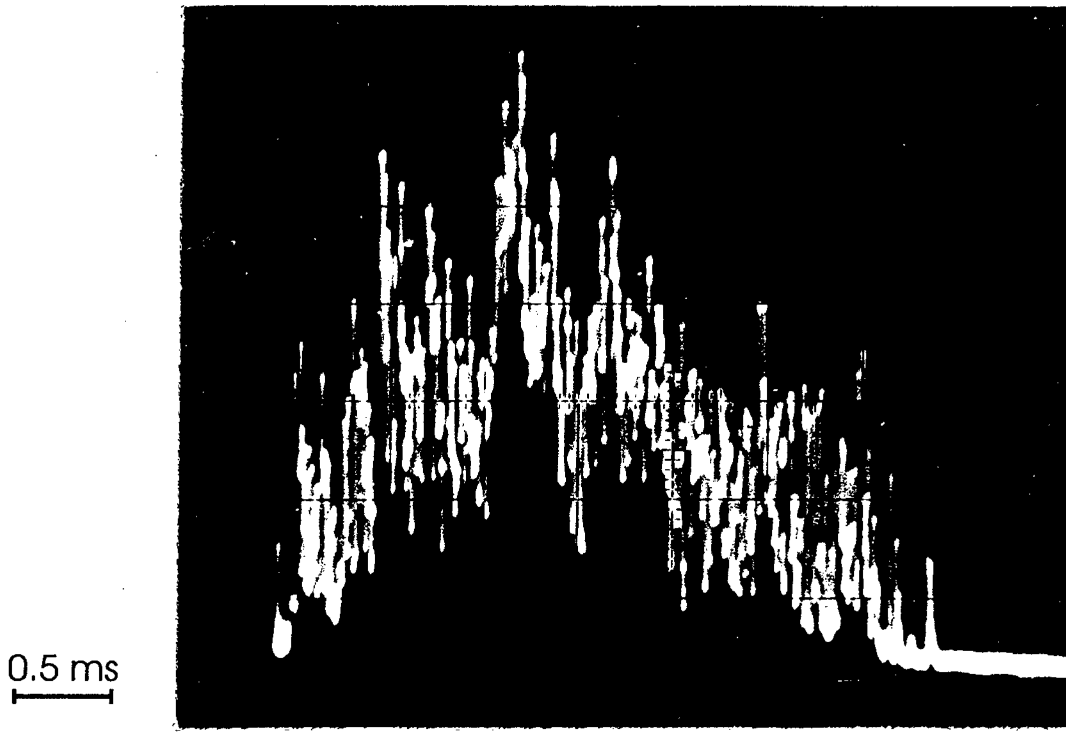


Fig.2. Temporal shape of the output of Er-glass laser in free running mode.

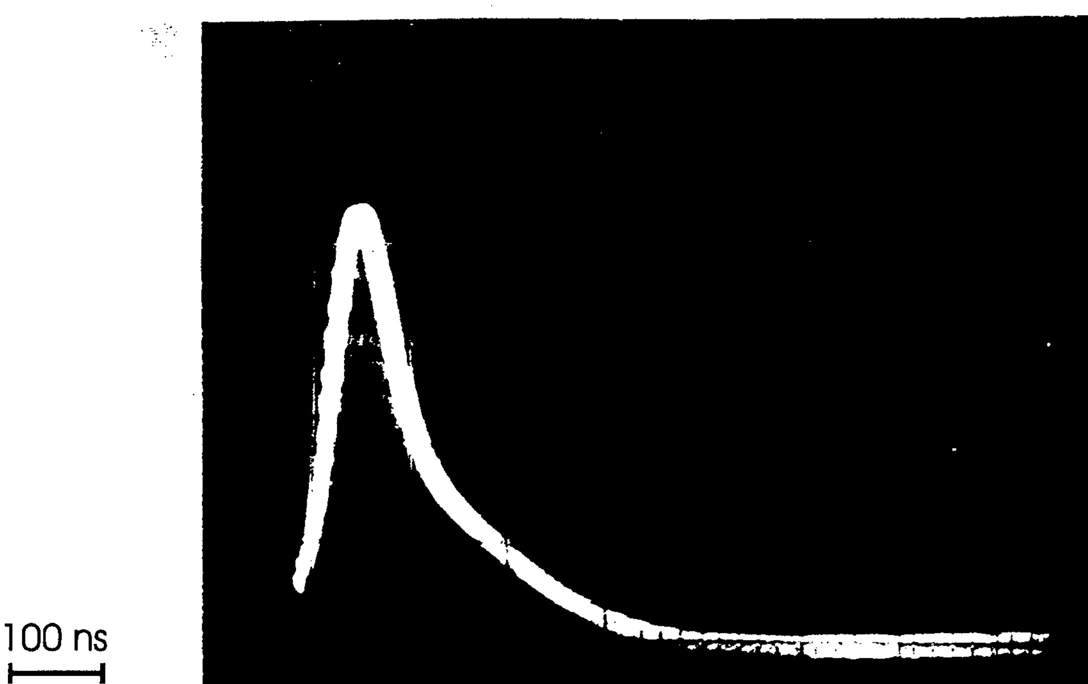
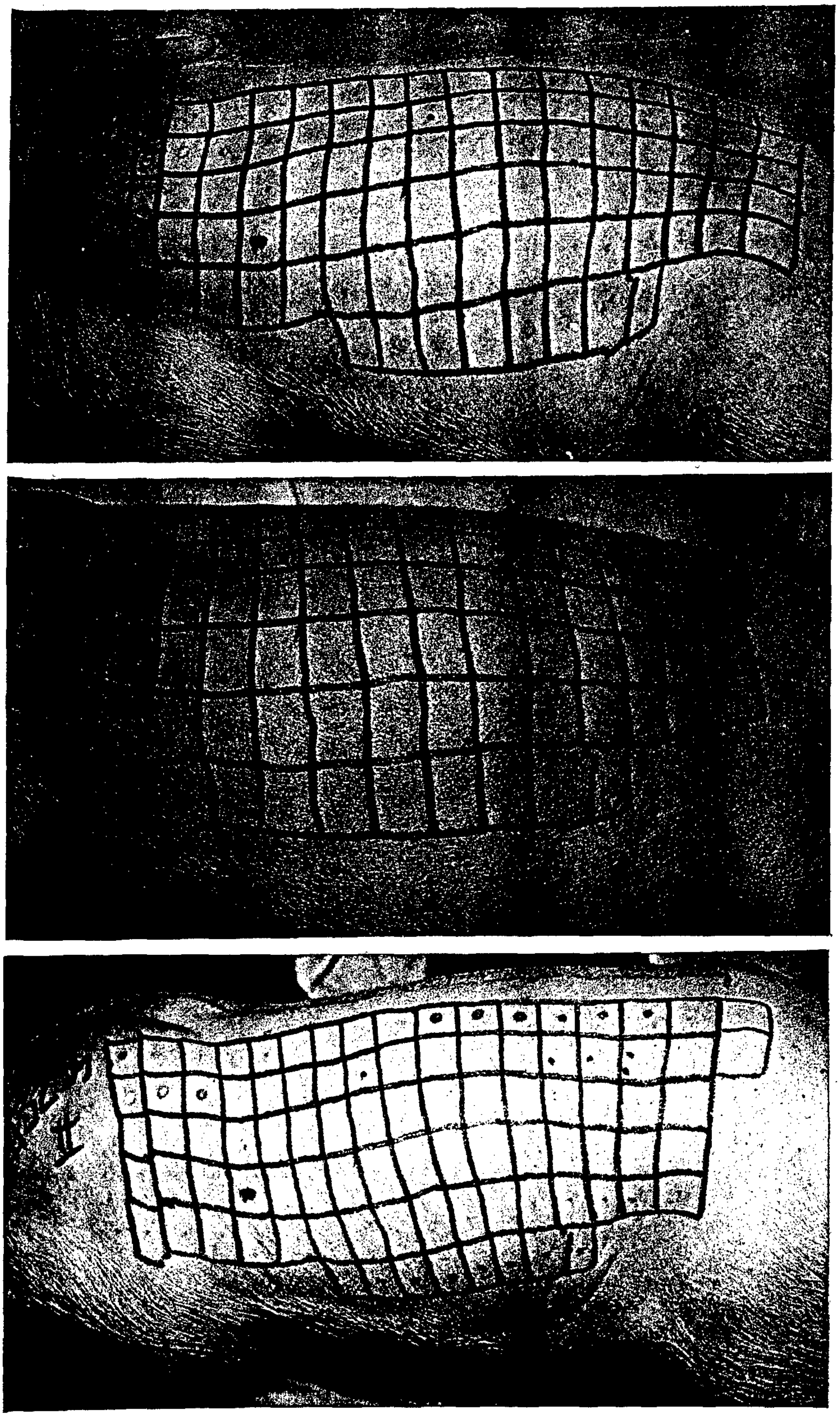


Fig.3. Temporal shape of the output of Er-glass laser in Q-switch mode.

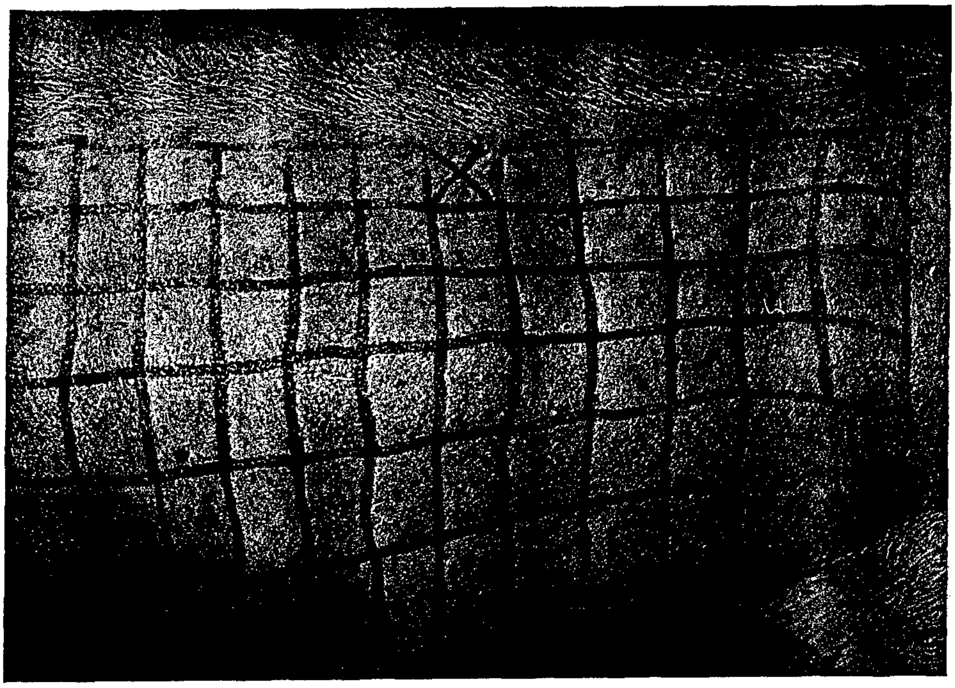


a

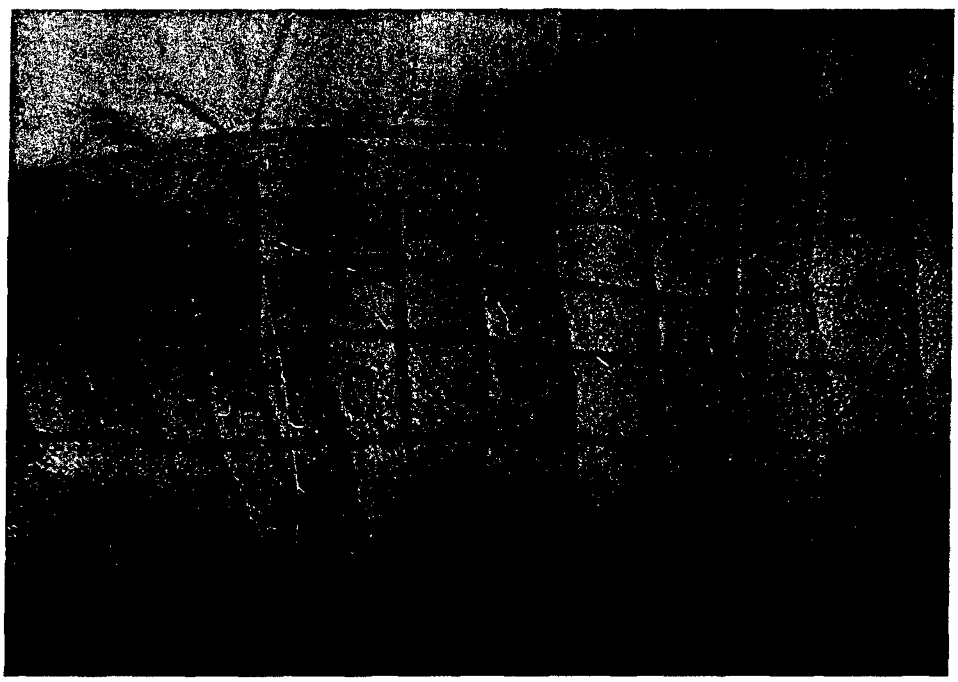
b

c

Fig.4. A view of skin lesions caused by free running radiation of Er-glass laser. **a** -5 minutes post-exposure(PE), **b** -1 hour PE, **c** -24 h PE.



a



b

Fig.5. A view of skin lesions caused by Q-switched radiation of Er-glass laser. **a** -1hour post-exposure(PE), **b** -24 h PE.

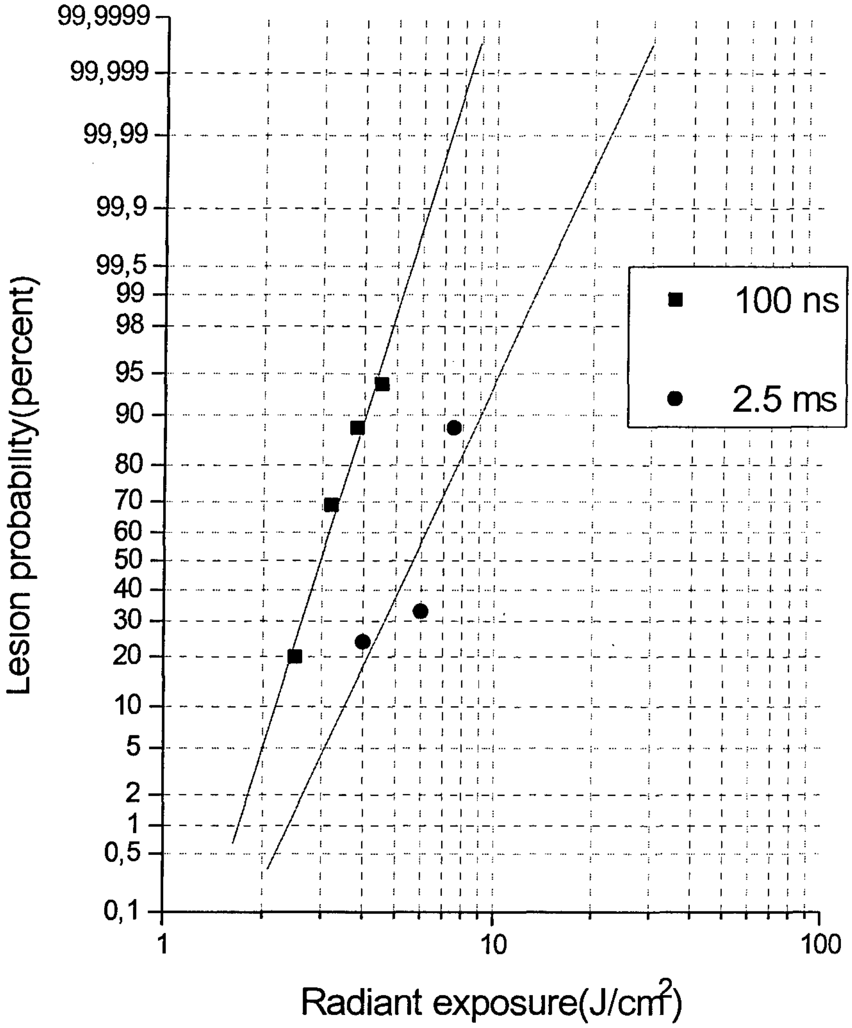
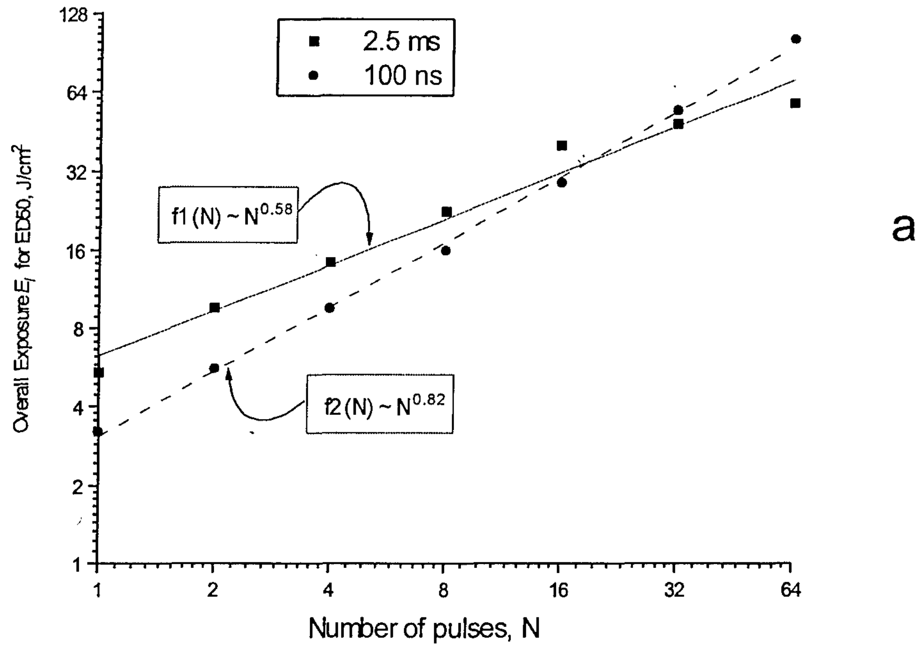


Fig.6. Dependence of the probability of minimal lesion(erythema) on skin caused by 1540 nm laser radiation upon laser energy fluence.



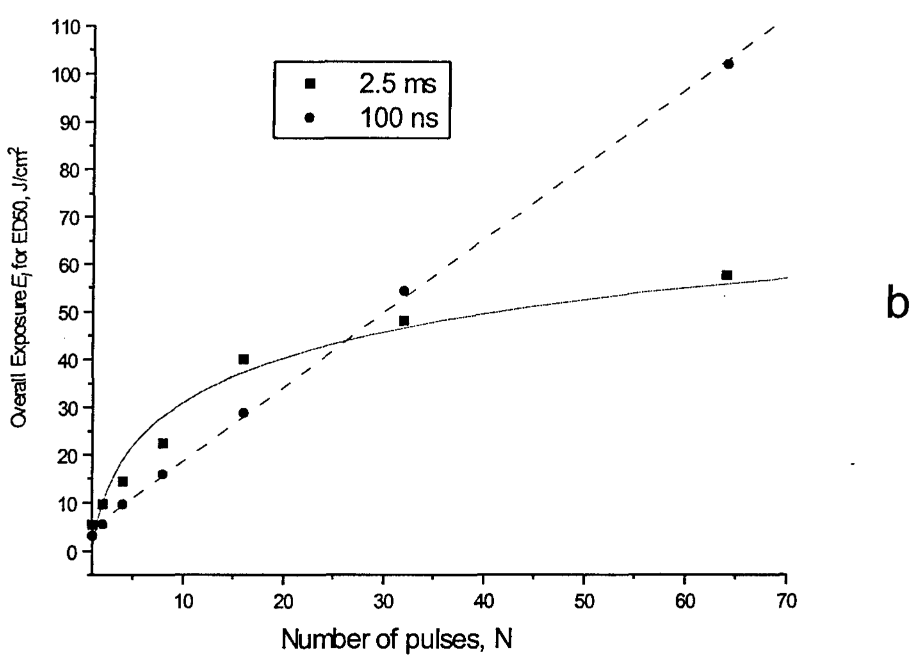
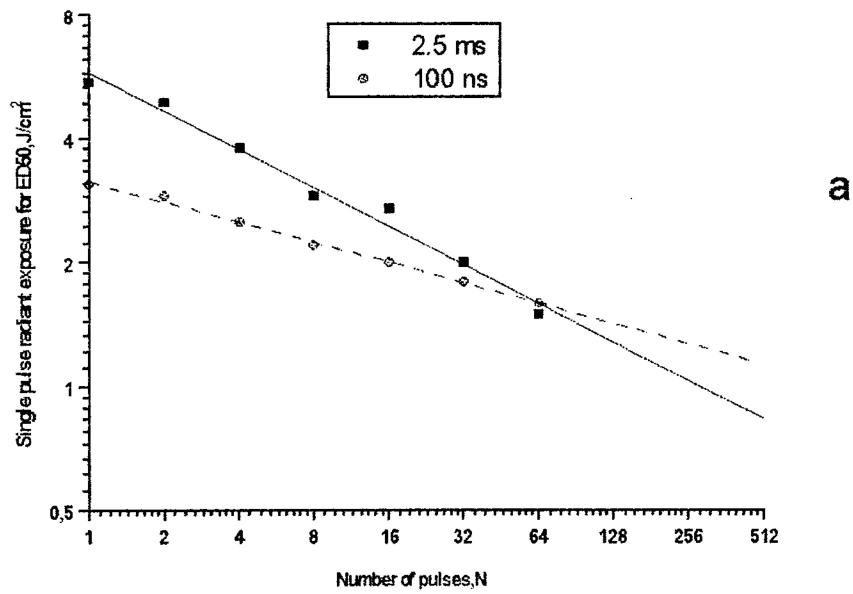


Fig.7. Dependence of overall exposure $E_I = E_{sp}N$, producing minimal lesion in 50% of the cases(ED50) upon number of pulses.
a - logarithmic scale, **b** - linear scale.



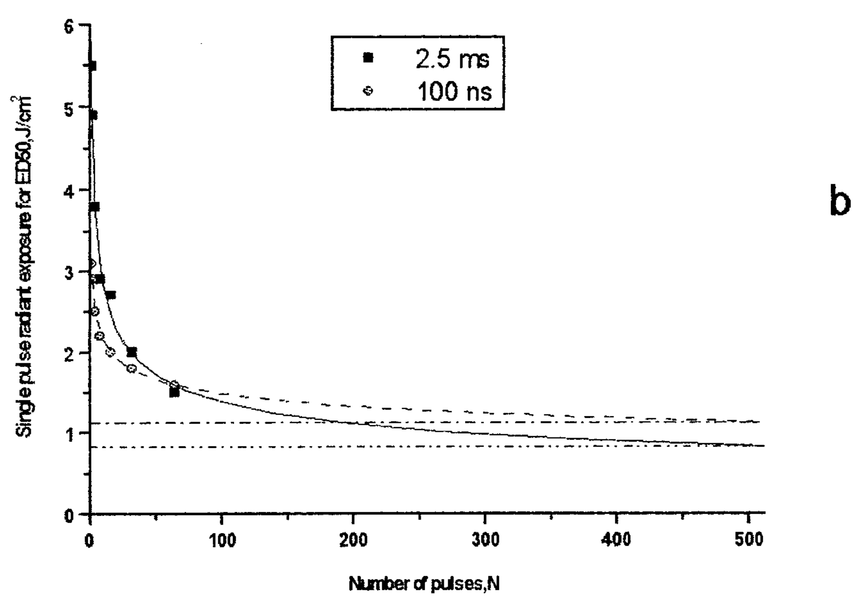


Fig.8. Dependence of single pulse energy fluence in the sequence of N repetitive pulses producing minimal lesion in 50% of the cases(ED50) at 24 h post exposure. **a** - logarithmic scale, **b** - linear scale.